SUTHERLAND

999 Peachtree St., N.E.
Atlanta, GA 30309-3996
404.853.8000 Fax 404.853.8806
www.sutherland.com

ATLANTA
AUSTIN
HOUSTON
NEW YORK
WASHINGTON DC

Facsimile

CONFIDENTIAL

Date: February 3, 2010 **Pages (including cover):** 8

TO:

Recipient Name	Firm/Company	Fax	Telephone
Examiner Lynn Bristol	U.S. Patent & Trademark Office	571.273.6883	571.272.6883

FROM: WILLIAM L. WARREN **Email address:** bill.warren@sutherland.com
Telephone: 404.853.8081 **User number:** 1295 **Client number:** 20825-0004

Message:

Re: U.S. Application No. 10/799,417
Applicant: Paul A. Krieg
Title: "METHODS FOR MODULATING ANGIOGENESIS WITH APELIN COMPOSITIONS"
Our Ref. No.: 20825-0004

Dear Examiner Bristol:

Pursuant to your request, enclosed are the claims recently granted by the EPO in the corresponding case. The EP case is proceeding to publication for opposition and nationalization. As discussed, the EPO does not directly allow direct method of treatment claims, but does allow "Swiss-type" claims which are modified to read as methods for the manufacture of a medicament for the treatment.

*Claims 1-10 are directed to in vitro methods of inhibiting angiogenesis.
***Claims 11-15 are directed to in vivo methods of (manufacture of a medicament for) treatment of a disease involving angiogenesis.**
*Claim 16 is a method for decreasing vascular permeability in vitro.
***Claims 17-18 are to methods of (manufacture of a medicament for) decreasing vascular permeability in vivo**
*Claims 19-22 are directed to promoting angiogenesis in vitro
***Claims 23-27 are to methods of (manufacture of a medicament for) promoting angiogenesis in vivo or treating a disease indicated by decreased vascularization in vivo.**
*Claims 28-29 are directed to methods of identifying a modulator of angiogenesis in vitro.

Regards,

William L. Warren
Reg. No. 36,714

36467P EP-WO/WWPBkd
04 720 472.2

Main Request
Claims 1-29

1. A method of inhibiting angiogenesis or tumorigenesis in vitro in a biological sample, comprising
   (a) providing a biological sample in vitro; and
   (b) combining the sample with an angiogenesis-inhibiting or tumorigenesis-inhibiting amount of a composition comprising an inhibitor of apelin activity, which is:
      (i) an anti-apelin antibody or fragment thereof,
      (ii) an anti-APJ antibody or fragment thereof, or
      (iii) an apelin antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor for apelin, or
      (iv) an APJ antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with APJ.

2. The method of Claim 1, wherein the composition decreases vascular permeability in the biological sample.

3. The method of Claim 1 or 2, wherein the composition interferes with the interaction of an apelin polypeptide or apelin peptide with a receptor polypeptide, particularly with APJ.

4. The method of any one of Claims 1 to 3 wherein the composition further comprises an anti-cancer agent and wherein the anti-cancer agent is selected from the group consisting of a chemotherapeutic agent, a radiotherapeutic agent, an anti-angiogenesis agent, and an apoptosis-

inducing agent.

5. The method of Claim 4, wherein the composition comprises an anti-angiogenesis agent that inhibits an angiogenic factor selected from the group consisting of VEGFs, FGFs, PDGFB, EGF, LPA, HGF, PD-ECF, IL-8, angiogenin, TNF-alpha, TGF-beta, TGF-alpha, proliferin, and PLGF.

6. The method of any one of claims 1 to 5, wherein the antibody or fragment thereof binds a polypeptide that is selected from the group consisting of:
   (a) a polypeptide as defined in SEQ ID NO:1;
   (b) a polypeptide as defined in SEQ ID NO:2;
   (c) a polypeptide as defined in SEQ ID NO:3;
   (d) a polypeptide as defined in SEQ ID NO:4, and
   (e) a polypeptide as defined in SEQ ID NO:5.

7. The method of any one of claims 1 to 5, wherein the antibody or fragment thereof binds a polypeptide selected from the group consisting of:
   (a) a polypeptide as defined in SEQ ID NO:17.

8. The method of any one of the preceding Claims, wherein the composition comprises a pharmaceutically acceptable carrier.

9. The method of any one of the preceding Claims, wherein the biological sample is from a mammal.

10. The method of Claim 9, wherein the biological sample is a human biological sample.

11. Use of an inhibitor of apelin activity for the manufacture of a medicament for the treatment of a disease or condition involving angiogenesis or

tumorigenesis, wherein the inhibitor of apelin activity is selected from:

(i) an anti-apelin antibody or fragment thereof,

(ii) an anti-APJ antibody or fragment thereof, or

(iii) an apelin antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor for apelin, or

(iv) an APJ antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with APJ.

12. The use of Claim 11, wherein the composition is suitable for introducing by a route selected from the group consisting of subcutaneous injection, intravenous injection, intraocular injection, intradermal injection, intramuscular injection, intraperitoneal injection, intratracheal administration, epidural administration, inhalation, intranasal administration, oral administration, sublingual administration, buccal administration, rectal administration, vaginal administration, and topical administration.

13. The use of Claim 11 or 12, wherein the disease or condition is selected from the group consisting of hemangioma, solid tumors, leukemias, lymphomas, myelomas, metastasis, telangiectasia, psoriasis, scleroderma, pyogenic granuloma, Myocardial angiogenesis, plaque neovascularization, coronary collaterals, ischemic limb angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, arthritis, diabetic neovascularization, macular degeneration, peptic ulcer, keloids, vasculogenesis, ovulation, menstruation, placentation, polycystic ovary syndrome, dysfunctional uterine bleeding, endometrial hyperplasia and carcinoma, endometriosis, myometrial fibroids (uterine leiomyomas) and adenomyosis, ovarian hyperstimulation syndrome, and ovarian carcinoma.

14. The use of any one of Claims 11-13, further comprising the use of a therapeutically effective amount of an anti-cancer agent,

wherein the anti-cancer agent is selected from the group consisting of a chemotherapeutic agent, a radiotherapeutic agent, an anti-angiogenic agent, an apoptosis-inducing agent.

15. The use of Claim 14, wherein the anti-angiogenic agent is an inhibitor of an angiogenic factor selected from the group consisting of VEGFs, FGFs, PDGFB, EGF, LPA, HGF, PD-ECF, IL-8, angiogenin, TNF-alpha, TGF-beta, TGF-alpha, proliferin, and PLGF.

16. A method of decreasing vascular permeability in vitro in a biological sample, comprising

(a) providing a biological sample in vitro; and

(b) combining the sample with a vascular permeability-decreasing amount of a composition comprising an inhibitor of apelin activity,

(i) an anti-apelin antibody or fragment thereof,

(ii) an anti-APJ antibody or fragment thereof, or

(iii) an apelin antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor for apelin, or

(iv) an APJ antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with APJ.

17. Use of an inhibitor of apelin activity for the manufacture of a medicament for decreasing vascular permeability, wherein the inhibitor of apelin activity is:

(i) an anti-apelin antibody or fragment thereof,

(ii) an anti-APJ antibody or fragment thereof, or

(iii) an apelin antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with the interaction of an apelin polypeptide or apelin peptide with a receptor for apelin, or

(iv) an APJ antisense nucleic acid, ribozyme, double stranded RNA, RNAi, and an aptamer, interfering with APJ.

18. The use of claim 17, wherein the disease or condition is selected from the group consisting of hemangioma, solid tumors, leukemias, lymphomas, myelomas, metastasis, telangiectasia, psoriasis, scleroderma, pyogenic granuloma, Myocardial angiogenesis, plaque neovascularization, coronary collaterals, ischemic limb angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, arthritis, diabetic neovascularization, macular degeneration, peptic ulcer, keloids, vasculogenesis, ovulation, menstruation, placentation, polycystic ovary syndrome, dysfunctional uterine bleeding, endometrial hyperplasia and carcinoma, endometriosis, myometrial fibroids (uterine leiomyomas) and adenomyosis, ovarian hyperstimulation syndrome, and ovarian carcinoma.

19. A method of promoting angiogenesis in vitro in a biological sample, comprising

(a) providing a biological sample in vitro; and

(b) combining the sample with a biologically effective amount of an angiogenesis promoting composition which comprises:

a polypeptide selected from the group consisting of:

(a) a polypeptide as defined in SEQ ID NO:1;

(b) a polypeptide as defined in SEQ ID NO:2;

(c) a polypeptide as defined in SEQ ID NO:3;

(d) a polypeptide as defined in SEQ ID NO:4; and

(e) a polypeptide as defined in SEQ ID NO:5.

20. The method of Claim 19, wherein the composition further comprises an angiogenic factor selected from the group consisting of VEGFs, FGFs, PDGFB, EGF, LPA, HGF, PD-ECF, IL-8, angiogenin, TNF-alpha, TGF-beta, TGF-alpha, proliferin, and PLGF.

21. The method of any one of Claims 19 to 20, wherein the biological sample is from a mammal.

22. The method of Claim 21, wherein the biological sample is a human biological sample.

23. Use of a composition for the manufacture of a medicament for promoting angiogenesis, wherein the composition comprises:
a polypeptide selected from the group consisting of:
(a) a polypeptide as defined in SEQ ID NO:1;
(b) a polypeptide as defined in SEQ ID NO:2;
(c) a polypeptide as defined in SEQ ID NO:3;
(d) a polypeptide as defined in SEQ ID NO:4; and
(e) a polypeptide as defined in SEQ ID NO:5.

24. Use of a composition for the manufacture of a medicament for the treatment of a disease or condition that is indicated by decreased vascularization, wherein the composition comprises:
a polypeptide selected from the group consisting of:
(a) a polypeptide as defined in SEQ ID NO:1;
(b) a polypeptide as defined in SEQ ID NO:2;
(c) a polypeptide as defined in SEQ ID NO:3;
(d) a polypeptide as defined in SEQ ID NO:4; and
(e) a polypeptide as defined in SEQ ID NO:5.

25. The use of Claim 24, wherein the disease or condition is selected from the group consisting of diabetes, arthritis, ischemia, anemia, a wound, gangrene, or necrosis.

26. The use of any one of Claims 23 to 25, wherein the composition is suitable for introduction by a route selected from the group consisting of subcutaneous injection, intravenous injection, intraocular injection, intradermal injection, intramuscular injection, intraperitoneal injection, intratracheal administration, epidural administration, inhalation, intranasal administration, oral administration, sublingual administration,

buccal administration, rectal administration, vaginal administration, and topical administration.

27. The use of any one of Claims 23 to 26, wherein the composition comprises a pharmaceutically acceptable carrier.

28. A method for identifying a modulator of angiogenesis, comprising
(a) providing an angiogenesis promoting composition comprising apelin;
(b) combining a putative modulator of angiogenesis with the composition;
(c) introducing the composition or the combination of the putative modulator and the composition to an angiogenesis predictive model; which is a chicken chorioallantoic membrane (CAM) assay and
(d) comparing the amount of vascular branching in the model in the presence and absence of the putative modulator.

29. The method of Claim 28, wherein the composition comprises a polypeptide selected from the group consisting of:
(a) a polypeptide as defined in SEQ ID NO:1;
(b) a polypeptide as defined in SEQ ID NO:2;
(c) a polypeptide as defined in SEQ ID NO:3;
(d) a polypeptide as defined in SEQ ID NO:4; and
(e) a polypeptide as defined in SEQ ID NO:5.